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AUTHOR(S):

Suzuki, Hitomi; Iwao, Tetsuya; Sugiyama, Takashi

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Note

**A Convenient Laboratory Method for the Preparation
of Thiophenecarbonitriles**

Hitomi SUZUKI*, Tetsuya IWAO**, and Takashi SUGIYAMA***

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In connection with the synthetic work on the thieno-heterocyclic systems, some substituted thiophenecarbonitriles and thiophenedicarbonitriles were needed. Previously reported routes to these compounds involve:

- dehydration of thenaloximes¹⁾ or thiophenecarboxamides.²⁾
- reaction of halothiophenes with metal cyanides.³⁾
- reaction of thiophenecarboxylic acids with chlorosulfonyl isocyanate.⁴⁾
- gas-phase oxidative ammonolysis of alkylthiophenes at high temperatures over transition metal catalysts.⁵⁾
- cyclization of S-cyanomethylated enethiols or thioacylmalonic acid derivatives.⁶⁾
- reaction of methylene active nitriles with carbonyl compounds and sulfur.⁷⁾

Besides, several special methods have been recorded.⁸⁾

Of all of these methods, the reaction of halothiophenes with cuprous cyanide (the Rosenmund-von Braun reaction) seemed to be of advantage for our purpose with respect to easy access to starting material, expense, and manipulative simplicity. The reaction has usually been accomplished by heating halothiophenes with cuprous cyanide at high temperatures, with or without organic bases such as pyridine or quinoline as promoter or solvent. Preliminary experiments, however, revealed that the reaction was not amenable to our compounds, since prolonged heating with cuprous cyanide at high temperatures led to the extensive formation of polymeric substance. Thus, with an intent to find milder conditions which can efficiently convert halothiophenes into thiophenecarbonitriles, the reactions have been examined in the presence of aprotic solvents, using simple halothiophenes as common substrate. The present note describes a method for the preparation of thiophenecarbonitriles, in which the above problem was circumvented.

Heating of iodothiophenes with cuprous cyanide in hexamethylphosphoric triamide (HMPA) at about 80–90°C for 2 to 3 hr was found to lead to the smooth replacement of

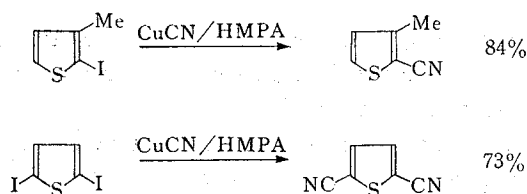
* 鈴木仁美: Department of Chemistry, Faculty of Science, Hiroshima University, Higashi-senda-machi, Hiroshima.

** 岩尾徹也: Department of Chemistry, Faculty of Science, Kyoto University, Kyoto.

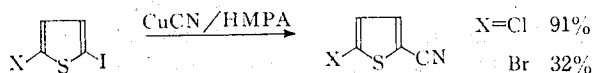
*** 杉山 卓: Laboratory of Organic Unit Reactions, Institute for Chemical Research, Kyoto University, Uji, Kyoto.

iodine atom by cyano group. Dilution of the reaction mixture with aqueous sodium cyanide, followed by extraction of nitrile with ether, removal of the solvent, and fractional distillation under reduced pressure readily gave a high yield of thiophenecarbonitriles. Great advantages in the use of HMPA as solvent are shortened reaction time and lowered temperature needed. The reaction was clean and mild, and little amorphous substance was formed. Catalysts were unnecessary.

Multiple replacement by cyano groups of iodine atoms on non-adjacent carbon atoms of thiophene nucleus can be effected with similar ease, giving the corresponding thiophenedicarbonitriles in high yields. Thus, 2,5-diiodothiophene and 2,5-diiodo-3-methylthiophene gave thiophene-2,5-dicarbonitrile and 3-methylthiophene-2,5-dicarbonitrile in 73% and 84% yields, respectively. The use of bromo compounds led to less satisfactory preparative results.



Taking advantage of the different reactivities of two dissimilar halogen atoms, 2-chloro-5-iodothiophene and 2-bromo-5-iodothiophene were converted into 5-chlorothiophene-2-carbonitrile and 5-bromothiophene-2-carbonitrile in 91% and 32% yields, respectively. The proton NMR spectrum indicated the presence of minor amounts of thiophene-2,5-dicarbonitrile and 5-iodothiophene-2-carbonitrile in the latter nitrile obtained. By carefully controlling the reaction time and temperature, it would be possible to suppress undesirable side-reactions and increase the yield of the bromonitrile.



This method is especially attractive for the laboratory preparation of acid and/or alkali sensitive, or thermally unstable thiophenecarbonitriles. Since various iodothiophenes are readily obtained by the direct iodination of the corresponding thiophenes with iodine/periodic acid,⁹⁾ the present procedure should provide a convenient and facile laboratory synthesis of a variety of the titled compounds.

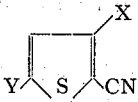
EXPERIMENTAL

Melting and boiling points are uncorrected. Infrared spectra were recorded on liquid film or Nujol mulls with a Jasco 402G spectrophotometer. Proton NMR spectra were obtained in deuteriochloroform or carbon tetrachloride with a Varian T-60 spectrometer against internal TMS. Commercial GR grades of cuprous cyanide and HMPA were used without further purification.

The structures of the compounds obtained were established by comparison with the

Preparation of Thiophenecarbonitriles

Table I. Yields and Physical Properties of Some Thiophenecarbonitriles

Compound	X	Y	Mp (°C)	Bp (°C)	Yield (%)	¹ H NMR Spectra (δ)	IR Spectra (cm ⁻¹)
	H	H		92- 94/27 mmHg	85	6.66-6.81 (m, H) 7.13-7.34 (m, 2H)	2230
	Me	H**		90- 91/16 mmHg	84	2.42 (s, 3H)* 6.92 (d, H; J=6 Hz) 7.43 (d, H; J=6 Hz)	2225
	H	Cl		93- 94/17 mmHg	91	6.45 (d, H; J=6 Hz)* 7.42 (d, H; J=6 Hz)	2225
	H	Br		114-117/15 mmHg	32	7.06 (d, H; J=4 Hz) 7.35 (d, H; J=4 Hz)	2225
	CN	H	103-104		73	7.61 (s, 2H)	2230
	Me	CN	73-74	137-138/16 mmHg	83	2.51 (s, 3H) 7.44 (s, H)	2225

* In deuteriochloroform solution.

** Found; C, 58.28; H, 4.06%. C₆H₅NS requires C, 58.51; H, 4.09%

literature data and in the case of newly prepared compounds, on the basis of the analyses, infrared and proton NMR spectra. The yields and physical characteristics of the thiophenecarbonitriles and thiophenedicarbonitriles are summarized in Table.

Procedure for the Iodination of Thiophenes

The general procedure is illustrated below by the reaction of 3-methylthiophene.

A mixture of 3-methylthiophene (4.91 g), periodic acid dihydrate (2.28 g), iodine (5.10 g), and 80% acetic acid (60 ml) containing catalytic amount of sulfuric acid was stirred and warmed at 60-65°C. The stirring was continued for 0.5 to 1 hr until the color of iodine had almost disappeared and a heavy oil had precipitated. Upon cooling, the mixture was diluted with water, the organic layer was taken up into ether, and the ethereal solution was distilled *in vacuo* after being washed with a dilute aqueous sodium hydrogen sulfite solution, and dried over anhydrous sodium sulfate. There was obtained a 72% yield (8.1 g) of 2-iodo-3-methylthiophene boiling at 49-51°C/2 mmHg; 123-125°C/70 mm Hg.¹⁰ IR: 1533, 1398, 1380, 1230, 920, and 705 cm⁻¹; ¹H NMR: δ 2.20 (s, 3H), 6.65 (d, H; J=6 Hz), and 7.24 (d, H; J=6 Hz).

By the use of double the amount of iodine and periodic acid dihydrate, 2,5-diiodo-3-methylthiophene was obtained in 65% yield. Bp 111-113°C/2 mmHg; 154-155°C/17 mmHg.¹¹ IR: 1393, 1378, 1186, 1016, 971, 896, 826 cm⁻¹; ¹H NMR: δ 2.17 (s, 3H), 6.81 (s, H).

2-Iodothiophene (bp 74-76°C/17 mmHg)¹², 2-chloro-5-iodothiophene (bp 96-97°C/17 mmHg)¹³, 2-bromo-5-iodothiophene (bp 116-118°C/17 mmHg),¹⁴ and 2,5-diiodothiophene (mp 40-42°C)¹⁵ were prepared in similar manner and yield from thiophene and its halo derivatives.

Procedure for the Conversion of Halothiophenes into Thiophenecarbonitriles

The procedures are illustrated by the preparations of 5-chlorothiophene-2-carbonit-

rile and 3-methylthiophene-2,5-dicarbonitrile. Although no attempts were made to optimize the reaction, the use of somewhat excess cuprous cyanide seems to give better results.

5-Chlorothiophene-2-Carbonitrile: A mixture of 2-chloro-5-iodothiophene (4.5 g), cuprous cyanide (1.8 g), and HMPA (ca. 4 ml) was heated with stirring at 80–90°C for 2 hr, and then poured into excess of aqueous sodium cyanide solution to decompose the complex. The precipitated oil was extracted with ether, the extract was thoroughly washed with water, dried over anhydrous sodium sulfate, and the solvent was evaporated. The residual oil was fractionally distilled *in vacuo* to give nitrile as pale yellow oil (2.4 g; 91%) boiling at 93–94°C/17 mmHg.¹⁶⁾

3-Methylthiophene-2,5-Dicarbonitrile: A mixture of 3-methyl-2,5-diiodothiophene (10.5 g),¹¹⁾ cuprous cyanide (6.2 g), and HMPA (ca. 5 ml) was heated with stirring at 80–90°C. After 1.5 to 2 hr, the dark mixture turned to a pasty solid, which was added to aqueous sodium cyanide solution. The resulting precipitate was extracted with ether, washed with water, and dried. After removal of the solvent, the residue was fractionally distilled under reduced pressure to give dinitrile as a pale yellow oil boiling at 137–138°C/16 mmHg, which soon turned to a crystalline solid (3.7 g; 83%). The solid was purified by recrystallization from a mixture of light petroleum and dichloromethane to give fine needles melting at 73–74°C.

Found: C, 56.82; H, 2.70; N, 18.71%.

C₇H₄N₂S requires C, 56.74; H, 2.72; N, 18.90%.

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